Complete Summary

GUIDELINE TITLE

(1) KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. (2) 2007 update of hemoglobin target.

BIBLIOGRAPHIC SOURCE(S)

KDOQI. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis 2007 Sep;50(3):471-530. [61 references] PubMed

National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease [published erratum Am J Kidney Dis 2006 Sep;48(3):518]. Am J Kidney Dis 2006 May;47(5 Suppl 3):S1-145. [461 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000. Am J Kidney Dis 2001 Jan;37(1 Suppl 1):S182-238.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating

serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Anemia of chronic kidney disease

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Nephrology
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel
Dietitians
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses

Pharmacists
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To describe the evidence base for key elements in the identification, evaluation, and management of patients with chronic kidney disease (CKD)-associated anemia

TARGET POPULATION

Adult and pediatric patients with chronic kidney disease (CKD) stages 1 to 5 not on dialysis therapy, on hemodialysis (HD) or peritoneal dialysis (PD) therapy, or with a kidney transplant in the full range of practice settings in which they are encountered

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Evaluation of anemia
    - Annual hemoglobin (Hb) levels
    - Complete blood count, including red blood cell indices, white blood cell count, and differential and platelet count
    - Absolute reticulocyte count
    - Serum ferritin
    - Serum transferrin saturation (TSAT) *or* content of Hb in reticulocytes (CHr)
2. Evaluation of patient hyporesponse to erythropoiesis-stimulating agent (ESA) therapy, including evaluation for pure red cell aplasia (PRCA)

Treatment/Management

Correction and maintenance of Hb levels using erythropoiesis-stimulating agents (epoetin alfa, epoetin beta, and darbepoetin alfa), iron agents, and/or transfusion therapy

Note: Use of pharmacological and nonpharmacological adjuvants to ESA treatment in hemodialysis (HD)-CKD patients was considered by the work group. However, the work group recommended against using androgen as an adjuvant to ESA therapy. There was insufficient evidence to recommend use of L-carnitine or vitamin C.

MAJOR OUTCOMES CONSIDERED

- Accuracy of evaluation of anemia in chronic kidney disease (CKD)
- Changes in markers of anemia, including hemoglobin (Hb) levels, serum ferritin levels, transferrin saturation (TSAT), and hematocrit (HCT)
- Changes in dosages of iron management agents

- Morbidity (including cardiovascular and cerebrovascular disease) and mortality due to anemia of chronic renal failure
- Patient survival
- Kidney disease progression
- Quality of life
- Neurocognitive effects
- Frequency of hospitalization
- Need for transfusion
- Adverse events due to treatment of anemia of chronic renal failure

2007 Addendum

- All-cause mortality
- Cardiovascular, cerebrovascular, and peripheral vascular disease
- Left ventricular hypertrophy
- Quality of life
- Hospitalizations
- Progression of kidney disease
- Dialysis adequacy
- Hypertension
- Transfusions
- Seizures

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

2006 Guideline

Literature Search

A master reference list was compiled from references used in previous evidence-based guidelines on anemia and chronic kidney disease (CKD):

1. European Best Practices Guidelines (EBPG) II, 2004
2. EBPG I, 2000
3. Kidney Disease Outcomes Quality Initiative (KDOQI) Anemia Guideline Update, 2000
4. Dialysis Outcomes Quality Initiative Anemia Guideline, 1997
5. Caring for Australasians with Renal Impairment (CARI) Anemia Guideline, 2003

For the topics addressed in EBPG II, update searches of MEDLINE were performed. For hemoglobin (Hb) Targets, a module for (Anemia and ESA and Kidney) was run on articles from January 2003 through March 2004. Selective updates of literature searches were performed through November 2004. A pre-MEDLINE search also was performed to capture more recent trials not yet indexed

in MEDLINE. For the topic of Iron Targets, the (Anemia and ESA and Kidney) module was modified by adding additional iron terms and was run to include publications between January 2003 and November 2004. For the topics of adjuvants to erythropoiesis-stimulating agent (ESA) treatment, a MEDLINE search was conducted for [(Anemia and Kidney) and (Androgens, Statins, Carnitine, Vitamin E, or Ascorbic Acid)] for all articles published from January 1989 through September 2004. A separate search for studies on prevalence of anemia by estimated glomerular filtration rate (eGFR) was conducted from January 1999 through February 2005. The searches also were supplemented by articles identified by Work Group members through September 2005.

Only full journal articles of original data were included. Editorials, letters, abstracts, and unpublished reports were not included. Selected review articles identified in the searches were provided to the Work Group for background material.

MEDLINE search results were screened by members of the evidence review team (ERT) for relevance by using predefined eligibility criteria, described in Table 44 in the original guideline document. Retrieved articles were screened by the ERT. Potentially relevant studies were sent to Work Group members for rescreening and data extraction. Domain experts, along with the ERT, made the final decision for inclusion or exclusion of all articles.

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched, and searches were limited to English-language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts that were missed by the electronic literature were added for consideration.

Literature Yield

For systematic review topics, the literature searches yielded 2,756 citations. Of these, 137 articles were reviewed in full. An additional 19 were added by Work Group members. A total of 83 were extracted and of these, 51 studies are included in Summary Tables. Details of the yield by topic can be found in Table 45 in the original guideline document.

The literature search yields for first-look topics can be found in Table 46 in the original guideline document. Upon reviewing the resultant abstracts, only the topics of noniron adjuvants (carnitine, ascorbic acid, and androgens) proceeded to systematic review.

2007 Addendum

For this guideline update, the Evidence Review Team (ERT) at Tufts-New England Medical Center in Boston, MA and the Work Group updated the systematic review of randomized controlled trials (RCTs) that compared the effect of targeting different hemoglobin (Hb) levels with ESA treatment. A detailed description of the methods can be found above. The inclusion criteria were: RCTs in patients with CKD stages 1 to 5, with a minimum of 2-month follow-up duration. Outcomes of interest were all-cause mortality; cardiovascular, cerebrovascular, and peripheral

vascular disease; left ventricular hypertrophy; quality of life; hospitalizations; progression of kidney disease; dialysis adequacy; hypertension; transfusions; and seizures.

An updated search conducted on December 7, 2006, with the previously used key words of KIDNEY and ANEMIA identified 639 citations of English-language studies indexed in MEDLINE after November 2004. Furthermore, the ERT searched the clinicaltrials.gov registration website to identify additional studies that might be completed. The search update resulted in the addition of 6 RCTs to the systematic review on this topic. All were in patients not on dialysis therapy, mostly with CKD stages 3 to 4.

NUMBER OF SOURCE DOCUMENTS

51 studies were included in Summary Tables for systematic review topics.

2007 Addendum

The search update resulted in the addition of 6 randomized controlled trials to the systematic review on the topic of hemoglobin target.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The quality of the overall body of evidence was determined based on the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each of the outcomes. To judge the balance between benefits and harms, the summaries for the actual results for each outcome were reviewed. Four grades for the quality of overall evidence were used.

Grade - Definition

High - Further research is unlikely to change the Work Group's confidence in the estimate of effect.

Moderate - Further research is likely to have an important impact on the Work Group's confidence in the estimate of effect and may change the estimate.

Low - Further research is very likely to have an important impact on the Work Group's confidence in the estimate of effect and may change the estimate.

Very Low - Any estimate of effect is very uncertain.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

2006 Guideline

Data Extraction

Data extraction forms were designed to capture information on various aspects of the primary studies. Data fields for all topics included study setting, demographics, eligibility criteria, causes of kidney disease, numbers of subjects, study design, study funding source, dialysis characteristics, comorbid conditions, descriptions of relevant risk factors or interventions, description of outcomes, statistical methods, results, study quality, study applicability, and free text field for comments and assessment of biases.

Evidence Tables

The evidence review team (ERT) condensed the information from the data extraction forms into evidence tables, which summarized individual studies. These tables were created for the Work Group members to assist them with review of the evidence and are not included in the original guideline document. All extracted articles and all evidence tables were made available to all Work Group members. During the development of the evidence tables, the ERT rescreened the accepted articles to verify that each of them met the initial screening criteria and checked the data extraction for accuracy. If the criteria were not met, the article was rejected, in consultation with the Work Group.

Summary Tables

Summary tables describe the studies according to the following dimensions: study size and follow-up duration, applicability or generalizability, results, and methodological quality (see Table 43 in the original guideline document). The ERT generated summary tables by using data from extraction forms, evidence tables, and/or the articles. All summary tables were reviewed by the Work Group members.

In the summary tables, studies were ordered first by method quality (best to worst), then by applicability (most to least), and then by study size (largest to smallest). Results are presented in their appropriate metric or in summary symbols, as defined in the table footnotes.

To provide consistency throughout summary tables, data sometimes were converted or estimated. Follow-up times were converted to months by estimating 1 month as 4 weeks. In general, data provided as percent hematocrit (Hct) was converted into grams per deciliter of hemoglobin (Hb) by dividing by 3. Additionally, results sometimes were estimated from graphs. All estimated values have been annotated as such.

Systematic Review Topics, Study Eligibility Criteria

The topics covered by systematic review are listed in Table 44 of the original guideline document. The screening criteria were defined by the Work Group members in conjunction with the ERT.

Assessment of Individual Studies

Study Size and Duration

The study (sample) size is used as a measure of the weight of a study. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to be generalizable; however, large size alone does not guarantee applicability. A study that enrolled a large number of selected patients may be less generalizable than several smaller studies that included a broad spectrum of patient populations. Similarly, longer duration studies may be of better quality and more applicable, depending on other factors.

Applicability

Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized to the population of interest at large. The study population typically is defined primarily by the inclusion and exclusion criteria. The target population was defined to include patients with anemia and kidney disease and subdivided into those with chronic kidney disease (CKD) stages 3 to 5 not on dialysis therapy and those with CKD stage 5 on hemodialysis (HD) or peritoneal dialysis (PD) therapy. Furthermore, one of the topics includes such special patient populations as kidney transplant recipients and patients with nonrenal anemias. Applicability was specified for each study according to a 3-level scale (Table 45A in the original guideline document). In making this assessment, sociodemographic characteristics were considered, as well as comorbid conditions and prior treatments. Applicability is graded in reference to the population of interest as defined in the clinical question. Target populations are specified in the titles of each summary table.

Study Quality

Method quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a 3-level classification of study quality was devised (Table 46A in the original guideline document).

<u>Quality of Studies of Interventions</u>

The evaluation of questions of interventions was limited to randomized controlled trials (RCTs). The grading of these studies included consideration of the methods (i.e., duration, degree of blinding, number and reasons for dropouts, and so on), population (i.e., does the population studied introduce bias?), outcomes (i.e., are the outcomes clearly defined and properly measured?), thoroughness/precision of reporting, statistical methods (i.e., was the study sufficiently powered and were the statistical methods valid?), and the funding source.

Quality of Studies of Prevalence

The ideal study design to assess prevalence of anemia and its association with estimated glomerular filtration rate (eGFR) is a cross-sectional study of a population representative of the general population. Criteria for evaluation of cross-sectional studies to assess prevalence are listed in Table 47 in the original guideline document.

Results

The type of results used from a study was determined by the study design, the purpose of the study, and the question(s) being asked for which the results were used. Decisions were based on the screening criteria and prespecified outcomes of interest (see Table 47 in the original guideline document).

Summarizing Reviews and Selected Original Articles

Work Group members had wide latitude in summarizing reviews and citing original articles.

2007 Addendum

The new studies were critically appraised by the ERT. The ERT extracted the data from these studies and added them to the summary tables published in the Kidney Disease Outcomes Quality Initiative (KDOQI) 2006 Anemia in CKD guidelines. Each study was graded with regard to its method quality. The Work Group experts reviewed and confirmed data and quality grades in the summary tables. The ERT and the Work Group members updated the evidence profiles for nondialysis patients following the modified Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach. The ERT tabulated an evidence matrix that provides an overview of the quality of the reviewed evidence. It tabulates all studies included in the review by type of outcome and quality.

Meta-analyses

Meta-analyses were performed on a subset of RCTs in the systematic review that had 6 or more months of mean follow-up. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for each study for mortality and for cardiovascular disease. For the cardiovascular disease end point, the ERT combined events for coronary, cerebrovascular, and peripheral vascular disease and heart failure as defined in each study. For CHOIR and CREATE, the ERT included all events from the primary composite outcomes, even though they also included deaths from any cause or from cardiac arrhythmias. Studies were grouped according to whether they were conducted in nondialysis patients or dialysis patients. One study was included with the dialysis studies, even though it contained a subgroup of nondialysis patients.

Calculations were performed using Meta-Analyst (version 0.99 1997; Joseph Lau, Tufts–New England Medical Center, Boston, MA). Because of the clinical heterogeneity of the studies in terms of populations, interventional protocols,

durations of follow-up, and outcome definitions, the ERT used a random-effects model according to DerSimonian and Laird for dichotomous outcomes. The random-effects model incorporates both within-study and between-studies variability in assigning weights to each study. It gives a wider CI when heterogeneity is present and thus is more conservative compared with a fixed-effect model.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

2006 Guideline

The lineage of the current document derives from both the 2001 version of the Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines for Anemia and the 2004 version of the European Best Practices Guidelines (EBPGs) for anemia. Key differences between current and past guidelines are set out in Table 1 of the original guideline document.

The Work Group sought to update the 2000 KDOQI clinical practice guidelines (CPGs) for Anemia of Chronic Kidney Disease (CKD) guidelines by using an evidence-based approach. After topics and relevant clinical questions were identified, the available scientific literature on those topics was systematically searched and summarized. High-quality or moderately high-quality evidence formed the basis for the development of evidence-based CPGs. When evidence was of low or very low quality or was entirely lacking, the Work Group could develop clinical practice recommendations (CPRs) based on consensus of expert opinion.

Creation of Groups

The KDOQI Co-Chairs appointed the Co-Chairs of the Work Group, who then assembled groups to be responsible for the development of the guidelines. The Work Group consisted of domain experts, including individuals with expertise in adult and pediatric nephrology, hematology, nursing and nutrition, cognitive function, quality of life (QOL), and cardiovascular disease (CVD) outcomes in patients with CKD. Support in evidence review and methods expertise was provided by an evidence review team (ERT) contracted by the National Kidney Foundation (NKF) at the NKF Center for Clinical Practice Guidelines Development and Implementation. The Work Group and the ERT collaborated closely throughout the project.

The first task of the Work Group members was to define the overall topics and goals for the update. Smaller groups of 2 to 4 individuals were formed and assigned to each topic. The Work Group and ERT then further developed and refined each topic and specified screening criteria for populations, interventions, predictors, comparisons groups and outcomes of interest and study design and minimum follow-up time criteria (PICOD), literature search strategies, and data

extraction forms. Work Group members were the principal reviewers of the literature, and from their reviews and detailed data extractions, they summarized the available evidence and took the primary roles of writing the guidelines and rationale statements.

The ERT consisted of individuals (staff, fellows, and research assistants) from Tufts-New England Medical Center with expertise in nephrology and development of evidence-based CPGs. It instructed the Work Group members in all steps of systematic review and critical literature appraisal. The ERT also coordinated the methodological and analytical process of the report; it defined and standardized the method of performing literature searches, data extraction, and summarizing the evidence in summary tables and evidence profiles. It performed literature searches, organized abstract and article screening, created forms to extract relevant data from articles, organized Work Group member data extraction, checked data, and tabulated results. Throughout the project, the ERT conducted seminars and provided instruction on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, and grading of the quality of evidence and strength of guideline recommendations.

Refinement of Topics and Development of Materials

The Work Group reviewed the 2000 KDOQI CPGs for Anemia of CKD and determined which of the guideline recommendations required updates and which could remain unchanged. These assessments were based primarily on expert opinion regarding the likelihood of new evidence being available. When experts were uncertain about the current evidence basis of a topic, a "first look" of the topic was undertaken to inform this process. After literature review of potentially relevant abstracts and studies, members of the Work Group focused the specific questions deemed clinically relevant and amenable to systematic review or decided to produce a narrative summary of the literature.

The Work Groups and ERT developed: (1) draft guideline statements, (2) draft rationale statements that summarized the expected pertinent evidence, and (3) data extraction forms requesting the data elements to be retrieved from the primary articles. The topic refinement process began before literature retrieval and continued through the process of reviewing individual articles.

Rating the Quality of Evidence and the Strength of Guideline Recommendations

A structured approach facilitated by the use of evidence profiles and modeled after the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach, was used to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the overall evidence and the strength of the recommendations was led by the primary expert reviewers of each topic, with participation by the Work Group chairs, all other Work Group members, and the ERT members.

Clinical Practice Recommendations for Anemia in Pediatric Patients with CKD

Given the distinct needs of pediatric patients, shared topics of concern among providers for both pediatric and adult patients, the generally low quality of evidence in pediatric patients, and the unavoidable need to generalize from evidence in adults, the Work Group chose to present CPRs in pediatric patients as a separate section, using adult guidelines as a frame of reference, changing recommendations when appropriate, and describing available evidence in pediatric patients under the guideline rationale.

2007 Addendum

This Update was developed using the usual rigorous methods of the KDOQI process, which involves a separate and independent ERT based at Tufts–New England Medical Center. This ERT evaluated and rated the available data, applying a priori–determined criteria about which new studies should and should not be included in the evidentiary base. Based on this review of the type and quality of data, the ERT also recommended which of the guideline statements should be considered for revision. The decision to update the 2006 Anemia Guidelines on hemoglobin (Hb) target was made in keeping with the KDOQI process, whereby new information did change the evidentiary base and thus the substance of some of the guidelines and CPRs. In contrast, the ERT and Work Group also considered an update of the iron guidelines and CPRs based on new studies. The statements on iron were not revised because the data from these studies did not meet prespecified criteria for evidence updates. The Methodology section of the original addendum document describes this process in more detail. The recommendations of the ERT for both the anemia and iron portions of the guidelines were reviewed by the Anemia Work Group, and the Work Group concurred with the ERT recommendations.

A meeting of the original 2006 KDOQI Anemia guidelines Work Group members, the ERT, and NKF support staff was held in Dallas, TX, on February 2 and 3, 2007. Before the face-to-face meeting in Dallas, all Work Group members and the KDOQI Chair and Vice-Chair completed new financial disclosure statements. Based on these financial disclosure statements, the Work Group chose the KDOQI Vice-Chair to moderate the face-to-face meeting in Dallas. The Work Group reviewed the summary tables; evidence profiles; U.S. Food and Drug Administration (FDA)-approved prescribing information for ESAs current as of March 2005 (Appendix 1 in the original addendum document); and the table of ongoing studies (Table 1 in the original addendum document). It then deliberated on what guideline recommendation the expanded evidence base would support. The Work Group then drafted recommendations and graded the strength of the recommendations. The strength of a guideline recommendation is shown in parentheses after the guideline statement as "strong" or "moderately strong." A "Clinical Practice Recommendation" is followed by "CPR" in parentheses. Issues considered in the grading of the quality of the evidence and the strength of the recommendations were detailed in the rationale section corresponding to each statement.

The draft of the updated guidelines underwent refinement and internal review by the Work Group by using emails and conference calls, subsequent review by the KDOQI Advisory Board and the public in April 2007, followed by further revisions by the Work Group.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Clinical Practice Guidelines (CPGs)

Strong - Indicates it is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is high quality evidence that the practice results in net medical benefit to the patient.

Moderately Strong - Indicates it is recommended that clinicians routinely follow the guideline for eligible patients. There is at least moderately high quality evidence that the practice results in net medical benefit to the patient.

Clinical Practice Recommendations (CPRs)

In the Opinion of the Work Group - In the absence of strong or moderately strong quality evidence or when additional considerations did not support strong or moderately strong evidence-based guideline recommendations, the Work Group could elect to issue CPRs based on consensus of expert opinions. These recommendations are based on the consensus of the Work Group that following the recommendations might improve health outcomes.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

2006 Guideline

This final version of the Clinical Practice Guidelines and Recommendations for Anemia has undergone revision in response to comments during the public review, an important and integral part of the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline process.

2007 Addendum

The draft of the updated guidelines underwent refinement and internal review by the Work Group by using emails and conference calls, subsequent review by the KDOQI Advisory Board and the public in April 2007, followed by further revisions by the Work Group.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI)*: In September 2007, NKF-KDOQI released an update to its 2006 Clinical Practice Guideline and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease, which updated the sections on hemoglobin targets. The affected sections are "CPG and CPR 2.1 Hemoglobin Target" and "CPR for Pediatrics 2.1 Hemoglobin Target." All other recommendations remain the same.*

Description of the grades of recommendation based on levels of evidence for clinical practice guidelines (CPGs) (Strong, Moderately Strong) and clinical practice recommendations (CPRs) (In the Opinion of the Work Group) and the definitions of the evidence grades (High, Moderate, Low, Very Low) are provided at the end of the "Major Recommendations" field.

Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease in Adults

CPR 1.1. Identifying Patients and Initiating Evaluation

Identifying anemia is the first step in evaluating the prognostic, diagnostic, and therapeutic significance of anemia in the patient with CKD.

1.1.1 Stage and cause of chronic kidney disease (CKD): In the opinion of the Work Group, hemoglobin (Hb) testing should be carried out in all patients with CKD, regardless of stage or cause.

1.1.2 Frequency of testing for anemia: In the opinion of the Work Group, Hb levels should be measured at least annually.

1.1.3 Diagnosis of anemia: In the opinion of the Work Group, diagnosis of anemia should be made and further evaluation should be undertaken at the following Hb concentrations:

- <13.5 g/dL in adult males
- <12.0 g/dL in adult females

CPR 1.2.: Evaluation Of Anemia In CKD

Anemia in patients with CKD is not always caused by erythropoietin deficiency alone. Initial laboratory evaluation therefore is aimed at identifying other factors that may cause or contribute to anemia or lead to ESA hyporesponsiveness.

1.2.1 In the opinion of the Work Group, initial assessment of anemia should include the following tests:

1.2.1.1 A complete blood count (CBC) including—in addition to the Hb concentration—red blood cell indices (mean corpuscular hemoglobin [MCH], mean corpuscular volume [MCV], mean corpuscular hemoglobin concentration [MCHC]), white blood cell count, and differential and platelet count.

1.2.1.2 Absolute reticulocyte count.

1.2.1.3 Serum ferritin to assess iron stores.

1.2.1.4 Serum transferrin saturation (TSAT) or content of Hb in reticulocytes (CHr) to assess adequacy of iron for erythropoiesis.

CPG and CPR 2.1. Hemoglobin Target (2007 Addendum)

The Hb target is the intended aim of erythropoiesis-stimulating agent (ESA) therapy for the individual patient with CKD. In clinical practice, achieved Hb results vary considerably from the Hb target.

2.1.1 In the opinion of the Work Group, selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events). (***Clinical Practice RECOMMENDATION***)

2.1.2 In the opinion of the Work Group, in dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. (***Clinical Practice RECOMMENDATION***)

2.1.3 In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL. (***Clinical Practice GUIDELINE – MODERATELY STRONG EVIDENCE***)

CPR 3.1. Using ESAs

ESAs are critical components in managing the anemia of CKD. Available ESAs are each effective in achieving and maintaining target Hb levels. Aspects of administration may differ between short-acting and long-acting agents.

3.1.1 Frequency of Hb monitoring:

3.1.1.1 In the opinion of the Work Group, the frequency of Hb monitoring in patients treated with ESAs should be at least monthly.

3.1.2 ESA dosing:

3.1.2.1 In the opinion of the Work Group, the initial ESA dose and ESA dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level, and clinical circumstances.

3.1.2.2 In the opinion of the Work Group, ESA doses should be decreased, but not necessarily withheld, when a downward adjustment of Hb level is needed.

3.1.2.3 In the opinion of the Work Group, scheduled ESA doses that have been missed should be replaced at the earliest possible opportunity.

3.1.2.4 In the opinion of the Work Group, ESA administration in ESA-dependent patients should continue during hospitalization.

3.1.2.5 In the opinion of the Work Group, hypertension, vascular access occlusion, inadequate dialysis, history of seizures, or compromised nutritional status are not contraindications to ESA therapy.

3.1.3 Route of administration:

3.1.3.1 In the opinion of the Work Group, the route of ESA administration should be determined by the CKD stage, treatment setting, efficacy, safety, and class of ESA used.

3.1.3.2 In the opinion of the Work Group, convenience favors subcutaneous administration in non-hemodialysis-CKD patients.

3.1.3.3 In the opinion of the Work Group, convenience favors intravenous (IV) administration in HD (hemodialysis)-CKD patients.

3.1.4 Frequency of administration:

3.1.4.1 In the opinion of the Work Group, frequency of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and class of ESA.

3.1.4.2 In the opinion of the Work Group, convenience favors less frequent administration, particularly in non-HD-CKD patients.

CPG and CPR 3.2. Using Iron Agents

Anemia therapy in patients with CKD requires effective use of iron agents, guided by appropriate testing of iron status. Efficacy of iron therapy appears not to be limited to patients with evidence of iron deficiency. (See Guideline 1.2 for diagnosis of iron deficiency.) Thus, the goals of iron therapy are to avoid storage iron depletion, prevent iron-deficient erythropoiesis, and achieve and maintain target Hb levels.

3.2.1 Frequency of iron status tests: In the opinion of the Work Group, iron status tests should be performed as follows:

3.2.1.1 Every month during initial ESA treatment.

3.2.1.2 At least every 3 months during stable ESA treatment or in patients with HD-CKD not treated with an ESA.

3.2.2 Interpretation of iron status tests: In the opinion of the Work Group, results of iron status tests, Hb, and ESA dose should be interpreted together to guide iron therapy.

3.2.3 Targets of iron therapy: In the opinion of the Work Group, sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment:

3.2.3.1 HD-CKD:

- Serum ferritin >200 ng/mL

  AND

- TSAT >20%, or CHr >29 pg/cell

3.2.3.2 Non-dialysis dependent (ND)-CKD and peritoneal dialysis-dependent (PD)-CKD:

- Serum ferritin >100 ng/mL

  AND

- TSAT >20%

3.2.4 Upper level of ferritin: In the opinion of the Work Group, there is insufficient evidence to recommend routine administration of IV iron if serum ferritin level is greater than 500 ng/mL. When ferritin level is greater than 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient's clinical status.

3.2.5 Route of administration:

3.2.5.1 The preferred route of administration is IV in patients with HD-CKD. (***STRONG RECOMMENDATION***)

3.2.5.2 In the opinion of the Work Group, the route of iron administration can be either IV or oral in patients with ND-CKD or PD-CKD.

3.2.6 Hypersensitivity reactions: In the opinion of the Work Group, resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.

CPG and CPR 3.3. Using Pharmacological and Nonpharmacological Adjuvants to ESA Treatment in HD-CKD

Several pharmacological agents and nonpharmacological manipulations of the HD prescription have been examined for potential efficacy as adjuvants to ESA treatment. Studies are not available to address the use of pharmacological or nonpharmacological adjuvants to ESA treatment in patients with ND-CKD and PD-CKD.

3.3.1 L-Carnitine: In the opinion of the Work Group, there is insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with CKD.

3.3.2 Vitamin C: In the opinion of the Work Group, there is insufficient evidence to recommend the use of vitamin C (ascorbate) in the management of anemia in patients with CKD.

3.3.3 Androgens: Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD. (***STRONG RECOMMENDATION***)

CPR 3.4.: Transfusion Therapy

Red blood cell transfusions should be used judiciously in patients with CKD, especially because of the potential development of sensitivity affecting future kidney transplantation. However, despite the use of ESA and iron therapy, transfusion with red blood cells occasionally is required, in particular in the setting of acute bleeding.

3.4.1 In the opinion of the Work Group, no single Hb concentration justifies or requires transfusion. In particular, the target Hb recommended for chronic anemia management (see Guideline 2.1) *should not serve as a transfusion trigger*.

CPR 3.5. Evaluating and Correcting Persistent Failure to Reach or Maintain Intended Hb

Although relative resistance to the effect of ESAs is a common problem in managing the anemia of patients with CKD and is the subject of intense interest, the bulk of available information suggests that – in the absence of iron deficiency – there are few readily reversible factors that contribute to ESA hyporesponsiveness.

3.5.1 Hyporesponse to ESA and iron therapy: In the opinion of the Work Group, the patient with anemia and CKD should undergo evaluation for specific causes of hyporesponse whenever the Hb level is inappropriately low for the ESA dose administered. Such conditions include, but are not limited to:

- A significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb level at a constant ESA dose
- A failure to increase the Hb level to greater than 11 g/dL despite an ESA dose equivalent to epoetin greater than 500 IU/kg/wk

3.5.2 Evaluation for pure red cell aplasia (PRCA): In the opinion of the Work Group, evaluation for antibody-mediated PRCA should be undertaken when a patient receiving ESA therapy for more than 4 weeks develops each of the following:

- Sudden rapid decrease in Hb level at the rate of 0.5 to 1.0 g/dL/wk, *or* requirement of red blood cell transfusions at the rate of approximately 1 to 2 per week

  AND

- Normal platelet and white blood cell counts

  AND

- Absolute reticulocyte count less than 10,000/microliter

Clinical Practice Recommendations for Anemia in Chronic Kidney Disease in Children

All statements in the pediatric section of the original guideline document assume the preface *In the opinion of the Work Group*, and all statements are provided as CPRs because there is insufficient evidence in pediatric patients to support evidence-based guidelines. When, in the opinion of the Work Group, the adult guideline statement applies equally well to adults and children, the statement is accompanied by the following: (***FULLY APPLICABLE TO CHILDREN***). When, in the opinion of the Work Group, the adult guideline statement needs modification or adjustment for children, the following instruction is given, followed by the pediatric-specific guideline statement: (***APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION***).

CPR for Pediatrics 1.1: Identifying Patients and Initiating Evaluation

Identifying anemia is the first step in evaluating the prognostic, diagnostic, and therapeutic significance of anemia in patients with CKD.

1.1.1 Stage and cause of CKD: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, Hb testing should be carried out in all patients with CKD, regardless of stage or cause.

1.1.2 Frequency of testing for anemia: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, Hb levels should be measured at least annually.

1.1.3 Diagnosis of anemia: (***APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION***)

ADULT CPR

In the opinion of the Work Group, diagnosis of anemia should be made and further evaluation should be undertaken at the following Hb concentrations:

- <13.5 g/dL in adult males
- <12.0 g/dL in adult females

PEDIATRIC CPR

In the opinion of the Work Group, in the pediatric patient, diagnosis of anemia should be made and further evaluation should be undertaken whenever the observed Hb concentration is less than the fifth percentile of normal when adjusted for age and sex.

CPR for Pediatrics 1.2: Evaluation of Anemia in CKD

Anemia in patients with CKD is not always caused by erythropoietin deficiency alone. Initial laboratory evaluation therefore is aimed at identifying other factors that may cause or contribute to anemia or lead to ESA hyporesponsiveness.

1.2.1 In the opinion of the Work Group, initial assessment of anemia should include the following tests: (***APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION***)

1.2.1.1 A CBC including-in addition to the Hb concentration-red blood cell indices (MCH, MCV, MCHC), white blood cell count and differential and platelet count.

1.2.1.2 Absolute reticulocyte count.

1.2.1.3 Serum ferritin to assess iron stores.

1.2.1.4 ADULT CPR
Serum TSAT *or* CHr to assess adequacy of iron for erythropoiesis.
PEDIATRIC CPR
In the pediatric patient, serum TSAT to assess adequacy of iron for erythropoiesis.

CPR for Pediatrics 2.1: Hemoglobin Target (2007 Addendum)

The Hb target is the intended aim of ESA therapy for the individual patient with CKD. In clinical practice, achieved Hb results vary considerably from the Hb target.

2.1.1 (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual pediatric patient should include consideration of potential benefits (including improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events). (***Clinical Practice RECOMMENDATION***)

2.1.2 (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, in pediatric dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. (***Clinical Practice RECOMMENDATION***)

2.1.3 (***APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION***) In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL. (***Clinical Practice RECOMMENDATION***)

CPR for Pediatrics 3.1: Using ESAs

ESAs are critical components in managing the anemia of patients with CKD. Available ESAs are each effective in achieving and maintaining target Hb levels. Aspects of administration may differ between short-acting and long-acting agents.

3.1.1 Frequency of Hb monitoring: (***FULLY APPLICABLE TO CHILDREN***)

3.1.1.1 In the opinion of the Work Group, the frequency of Hb monitoring in patients treated with ESAs should be at least monthly.

3.1.2 ESA dosing: (***FULLY APPLICABLE TO CHILDREN***)

3.1.2.1 In the opinion of the Work Group, the initial ESA dose and ESA dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in the Hb level, and clinical circumstances.

3.1.2.2 In the opinion of the Work Group, ESA doses should be decreased, but not necessarily held, when a downward adjustment of Hb level is needed.

3.1.2.3 In the opinion of the Work Group, scheduled ESA doses that have been missed should be replaced at the earliest possible opportunity.

3.1.2.4 In the opinion of the Work Group, ESA administration in ESA-dependent patients should continue during hospitalization.

3.1.2.5 In the opinion of the Work Group, hypertension, vascular access occlusion, inadequate dialysis, history of seizures, or compromised nutritional status are not contraindications to ESA therapy.

3.1.3 Route of administration: (***APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION***)

3.1.3.1 ADULT CPR
In the opinion of the Work Group, the route of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and the class of ESA used.
PEDIATRIC CPR
In the opinion of the Work Group, in the pediatric patient, the route of administration should be determined by the CKD stage, treatment setting, efficacy considerations, the class of ESA used, and the anticipated frequency and pain of administration.

3.1.3.2 In the opinion of the Work Group, convenience favors subcutaneous administration in non-HD-CKD patients.

3.1.3.3 In the opinion of the Work Group, convenience favors IV administration in patients with HD-CKD.

3.1.4 Frequency of administration: (***APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION***)

3.1.4.1 ADULT CPR
In the opinion of the Work Group, frequency of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and class of ESA.
PEDIATRIC CPR
In the opinion of the Work Group, in the pediatric patient, the frequency of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and class of ESA; as well, consideration should be given to the anticipated frequency of, and pain on administration of each agent and their potential effects on the child and family.

3.1.4.2 In the opinion of the Work Group, convenience favors less frequent administration, particularly in non–HD-CKD patients.

CPR For Pediatrics 3.2: Using Iron Agents

Anemia therapy in patients with CKD requires effective use of iron agents, guided by appropriate testing of iron status. Efficacy of iron therapy appears not to be limited to patients with evidence of iron deficiency. (See Guideline 1.2 for diagnosis of iron deficiency.) Thus, the goals of iron therapy are to avoid storage iron depletion, prevent iron-deficient erythropoiesis, and achieve and maintain target Hb levels.

3.2.1 Frequency of iron status tests: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, iron status tests should be performed as follows:

3.2.1.1 Every month during initial ESA treatment.

3.2.1.2 At least every 3 months during stable ESA treatment or in patients with HD-CKD not treated with an ESA.

3.2.2 Interpretation of iron status tests: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, results of iron status tests, Hb level, and ESA dose should be interpreted together to guide iron therapy.

3.2.3 Targets of iron therapy: (***APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION***) In the opinion of the Work Group, sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment:

3.2.3.1 <u>ADULT CPR</u> HD-CKD:

- Serum ferritin >200 ng/mL

  AND

- TSAT >20%, or CHr >29 pg/cell

<u>PEDIATRIC CPR</u> *HD-CKD*:

- Serum ferritin >100 ng/mL

  AND

- TSAT >20%

3.2.3.2 ND-CKD and PD-CKD:

- Serum ferritin >100 ng/mL

  AND

- TSAT >20%

3.2.4 Upper level of ferritin: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, there is insufficient evidence to recommend routine administration of IV iron if serum ferritin is greater than 500 ng/mL. When ferritin level is greater than 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient's clinical status.

3.2.5 Route of administration: (***FULLY APPLICABLE TO CHILDREN***)

3.2.5.1 The preferred route of administration is IV in patients with HD-CKD. (***STRONG RECOMMENDATION***)

3.2.5.2 In the opinion of the Work Group, the route of iron administration can be either IV or oral in patients with ND-CKD and PD-CKD.

3.2.6 Hypersensitivity reactions: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.

CPR for Pediatrics 3.3: Using Pharmacological and Nonpharmacological Adjuvants to ESA Treatment in HD-CKD

Several pharmacological agents and nonpharmacological manipulations of the HD prescription have been examined for potential efficacy as adjuvants to ESA treatment. Studies are not available to address the use of pharmacological or nonpharmacological adjuvants to ESA treatment in patients with ND-CKD and PD-CKD.

3.3.1 L-carnitine: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, there is insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with CKD.

3.3.2 Vitamin C: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, there is insufficient evidence to recommend the use of vitamin C (ascorbate) in the management of anemia in patients with CKD.

3.3.3 Androgens: (***FULLY APPLICABLE TO CHILDREN***) Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD. (***STRONG RECOMMENDATION***)

CPR for Pediatrics 3.4: Transfusion Therapy

Red blood cell transfusions should be used judiciously in patients with CKD, especially because of the potential development of sensitivity, affecting future kidney transplantation. However, despite the use of ESA and iron therapy, transfusion with red blood cells occasionally is required, in particular in the setting of acute bleeding.

3.4.1 (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, no single Hb concentration justifies or requires transfusion. In particular, the target Hb recommended for chronic anemia management (see Guideline 2.1) should not serve as a transfusion trigger.

CPR for Pediatrics 3.5: Evaluating and Correcting Persistent Failure to Reach or Maintain Intended Hb Level

Although relative resistance to the effect of ESAs is a common problem in managing the anemia of CKD and is the subject of intense interest, the bulk of available information suggests that--in the absence of iron deficiency--there are few readily reversible factors that contribute to ESA hyporesponsiveness.

3.5.1 Hyporesponse to ESA and iron therapy: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, the patient with anemia and CKD should undergo evaluation for specific causes of hyporesponse whenever the Hb level is inappropriately low for the ESA dose administered. Such conditions include, but are not limited to:

- A significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb levels at a constant ESA dose.
- A failure to increase the Hb level to greater than 11 g/dL despite an ESA dose equivalent to epoetin greater than 500 IU/kg/wk.

3.5.2 Evaluation for PRCA: (***FULLY APPLICABLE TO CHILDREN***) In the opinion of the Work Group, evaluation for antibody-mediated PRCA should be undertaken when a patient receiving ESA therapy for more than 4 weeks develops each of the following:

- Sudden rapid decline in Hb level at the rate of 0.5 to 1.0 g/dL/wk, *or* requirement of red blood cell transfusions at the rate of approximately 1 to 2 per week

  AND

- Normal platelet and white blood cell counts

  AND

- Absolute reticulocyte count less than 10,000/microliter

Clinical Practice Recommendations for Anemia in Chronic Kidney Disease in Transplant Recipients

See the original guideline document for a discussion of anemia in CKD in transplant recipients.

Definitions:

Clinical Practice Guidelines (CPGs)

Strong - Indicates it is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is high quality evidence that the practice results in net medical benefit to the patient.

Moderately Strong - Indicates it is recommended that clinicians routinely follow the guideline for eligible patients. There is at least moderately high quality evidence that the practice results in net medical benefit to the patient.

Clinical Practice Recommendations (CPRs)

In the Opinion of the Work Group - In the absence of strong or moderately strong quality evidence or when additional considerations did not support strong or moderately strong evidence-based guideline recommendations, the Work Group could elect to issue CPRs based on consensus of expert opinions. These recommendations are based on the consensus of the Work Group that following the recommendations might improve health outcomes.

Evidence Grade - Definitions

High - Further research is unlikely to change the Work Group's confidence in the estimate of effect.

Moderate - Further research is likely to have an important impact on the Work Group's confidence in the estimate of effect and may change the estimate.

Low - Further research is very likely to have an important impact on the Work Group's confidence in the estimate of effect and may change the estimate.

Very Low - Any estimate of effect is very uncertain.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Decreased morbidity due to anemia in chronic kidney disease
- Improved survival
- Improved quality of life

POTENTIAL HARMS

- All forms of intravenous (IV) iron may be associated with acute adverse events (AEs), occasionally severe, comprised of hypotension with or without other symptoms and signs. The cause of the reactions is incompletely understood. Immune mechanisms (including mast cell-mediated processes leading to a clinical syndrome resembling anaphylaxis) may have a role in some cases. In others, the iron agent may release bioactive, partially unbound iron into the circulation, resulting in oxidative stress and hypotension (labile or free iron reactions). The pathogenesis may differ depending on the type of IV iron. Anaphylactoid reactions appear to occur more frequently with iron dextran, and labile or free iron reactions occur more frequently with nondextran forms of iron.
- In general, risks per unit of red blood cells transfused are the same as in any setting. A number of retrospective studies have identified risks related to aggressive transfusion support. A review of patients with acute coronary artery syndromes revealed a greater mortality rate in transfusion recipients. In the presence of severe chronic anemia, transfusion may lead to congestive heart failure, particularly in the elderly. In such cases, red blood cell transfusions must be administered very slowly, and, in patients with hemodialysis-dependent chronic kidney disease (HD-CKD), transfusion during hemofiltration may be required. The administration of many red blood cell transfusions over a prolonged period can eventually lead to iron overload.
- Hypertension and seizures were noted in the first 3 months after initiating therapy with erythropoiesis-stimulating agents (ESAs) in severely anemic patients, but it is unclear whether these events occurred within the first 4 weeks and whether they were related to the rate of increase in hemoglobin levels.
- Among patients with HD-CKD, either subcutaneous (SC) or intravenous (IV) administration of ESAs is feasible, but the risk for pure red cell aplasia (PRCA) associated with SC administration, albeit small, recently prompted the US Food and Drug Administration (FDA) to recommend the IV route. The relationship between SC ESA administration and risk for PRCA experienced outside the United States is discussed in the original guideline document (Guideline 3.5).
- The development or worsening of hypertension during treatment with ESAs in children is of significant concern. In a study of children aged 4 months to 21 years, assignment to either high dose (epoetin, 450 IU/kg/wk) or low-dose (150 IU/kg/wk) ESA treatment was associated with a significant increase in diastolic blood pressure by week 12 compared with baseline (88 $\pm$ 6.7 versus 68 $\pm$ 17 mm Hg; paired t-test, P = 0.01). The investigators reported a nonsignificant trend between increasing Hb levels and increasing systolic and diastolic blood pressures despite stable or lower ESA dose.
- One concern in the use of IV iron in children, especially in an outpatient setting, is the potentially fatal acute AEs. All forms of IV iron may be associated with acute AEs, which may include hypotension, anaphylactoid reactions, and a variety of other symptoms. Immune mechanisms with activation of mast cells or release of bioactive partially unbound iron into the circulation resulting in oxidative stress and hypotension (labile or free iron reactions) are both possible mechanisms, and the underlying cause may differ depending on the type of IV iron. Anaphylactoid reactions appear to occur more frequently with iron dextran, and labile or free iron reactions, more frequently with nondextran forms of iron.

- Red blood cell transfusions, at least in the critically ill pediatric patient, may not be "benign" therapy. This was highlighted by a retrospective cohort study of 240 children in 5 pediatric intensive care units, 130 of whom received red blood cell transfusions. The study showed that even after controlling for a number of factors, such transfusions were associated with increased use of oxygen, days of mechanical ventilation, vasoactive agent infusions, length of intensive care unit stay, and total length of hospital stay.
- Adverse events thought to be related to labile iron agents require a decrease in the dose or rate of infusion or both. Adverse events thought to be related to hypersensitivity to the agent require stopping the agent and preclude further administration.

CONTRAINDICATIONS

CONTRAINDICATIONS

- *Androgens* should not be used as an adjuvant to erythropoietin-stimulating agent (ESA) treatment in anemic patients with chronic kidney disease (CKD).
- Multidose vials of *epoetin alfa* should be avoided if at all possible in premature infants and newborns because of a rare, but well-recognized, complication from the use of benzyl alcohol in the preparation of the compound. This excipient has been described to cause numerous serious and potentially fatal reactions, including metabolic acidosis, intraventricular hemorrhage, and neurological problems. Sixteen neonatal deaths were reported that were thought to be caused by benzyl alcohol toxicity, generally described as the so-called "gasping syndrome."

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These Clinical Practice Guidelines (CPG) and Clinical Practice Recommendations (CPRs) are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.
- Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health care professional making use of these CPG and CPRs is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

Guideline Limitations

See the "Limitations" sections for each guideline in the original guideline document and addendum for information on limitations of the available evidence.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation is an integral component of the Kidney Disease Outcomes Quality Initiative process, and accounts for the success of its past guidelines. The Kidney Learning System (KLS) component of the National Kidney Foundation is developing implementation tools that will be essential to the success of these guidelines.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Personal Digital Assistant (PDA) Downloads
Quick Reference Guides/Physician Guides
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

KDOQI. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis 2007 Sep;50(3):471-530. [61 references] PubMed

National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease [published erratum Am J Kidney Dis 2006 Sep;48(3):518]. Am J Kidney Dis 2006 May;47(5 Suppl 3):S1-145. [461 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 (updated 2006 May; addendum released 2007 Sep)

GUIDELINE DEVELOPER(S)

National Kidney Foundation - Disease Specific Society

SOURCE(S) OF FUNDING

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GUIDELINE COMMITTEE

NKF-KDOQI (National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) Anemia in Chronic Kidney Disease Working Group

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The National Kidney Foundation (NKF) makes every effort to avoid actual conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group.

Based on the Foundation's conflict-of-interest policy, all members of the Work Group are required to complete, sign, and submit a Disclosure Form and Attestation Statement showing all such relationships that might be perceived as real or potential conflicts of interest. Affiliations are published in their entirety in the section of this document titled Biographical and Disclosure Information and are kept on file at the NKF.

Please refer to "Biographical & Disclosure Information" section of the original guideline and addendum documents.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000. Am J Kidney Dis 2001 Jan;37(1 Suppl 1):S182-238.

GUIDELINE AVAILABILITY

Electronic copies of the 2006 guideline: Available from the National Kidney Foundation (NKF) Web site.

Electronic copies of the 2007 addendum: Available from the National Kidney Foundation (NKF) Web site.

Print copies: Available from the National Kidney Foundation (NKF), 30 East 33rd St., New York, NY 10016. These guidelines are also available on CD-ROM from NKF.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Management of Anemia in Chronic Kidney Disease in Adults
- Dialysis Care Package

Electronic and print copies can be ordered through the National Kidney Foundation (NKF) Web site.

The National Kidney Foundation provides a variety of additional companion documents and implementation tools in print and electronic form (CD-ROM/PDA software) to accompany this guideline. For more information contact: National Kidney Foundation 30 East 33rd Street, New York, NY 10016 (phone: 212.889.2210 or 800.622.9010 or fax: 212.686.8916) or go to the National Kidney Foundation Web site.

PATIENT RESOURCES

The following are available:

- Anemia and chronic kidney disease. Stages 1-4. (also available in Spanish)
- Managing anemia when you are on dialysis. Stage 5. (also available in Spanish)
- People like us: EPO treating anemia (also available in Spanish)
- Understanding anemia in CKD (CD-ROM/VHS video; also available in Spanish)
- What you need to know about anemia and chronic kidney disease

These patient education materials are available by contacting: National Kidney Foundation 30 East 33rd Street, New York, NY 10016 (phone: 212.889.2210 or 800.622.9010 or fax: 212.686.8916), or through the National Kidney Foundation Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on September 1, 2001. The information was verified by the guideline developer as of November 19, 2001. This summary was updated by ECRI on December 5, 2005, following the U.S. Food and Drug Administration advisory on Aranesp, Epogen, and Procrit. This NGC summary was updated by ECRI on September 13, 2006. The updated information was verified by the guideline developer on November 29, 2006. This summary was updated by ECRI on January 29, 2007, following the U.S. Food and Drug Administration advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents. This NGC summary was updated by ECRI Institute on December 10, 2007. The updated information was verified by the guideline developer on January 18, 2008. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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Date Modified: 10/6/2008